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1: Jpn J Pharmacol. 2000 Mar;82(3):188-98.



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Antiplatelet and antithrombotic effects of a novel selective phosphodiesterase 3 inhibitor, NSP-513, in mice and rats.

Hirose H, Kimura T, Okada M, Itoh Y, Ishida E, Mochizuki N, Nishibe T, Nishikibe M.

Tsukuba Research Institute, Banyu Pharmaceutical Co., Ltd., Okubo, Japan.

We investigated the effects of NSP-513, (R)-4,5-dihydro-5-methyl-6-[4-(2-propyl-3-oxo-1-cyclohexenyl)amino] phenyl-3 (2H)-pyridazinone, on phosphodiesterase (PDE) isozyme activities, in vitro platelet aggregation and in vivo thrombus formation. NSP-513 selectively inhibited human platelet PDE 3 isozyme with an IC50 value of 0.039 microM. In an in vitro human platelet aggregation assay, the IC50 values (microM) of NSP-513 for platelet aggregation induced by collagen, U-46619, arachidonic acid, adenosine diphosphate (ADP), epinephrine and thrombin were 0.31, 0.25, 0.082, 0.66, 0.23 and 0.73, respectively. In a mouse pulmonary thromboembolism model, orally administered NSP-513 showed in vivo antithrombotic effects that were 320 to 470 times more potent than those of cilostazol. In a rat carotid arterial thrombosis model, intraduodenally administered NSP-513 (0.1 mg/kg), cilostazol (30 mg/kg) and aspirin (30 mg/kg) reduced thrombus formation by 75%, 66% and 48%, respectively. However, intravenously administered dipyridamole (10 mg/kg) did not significantly prevent thrombus formation. These results demonstrate that NSP-513 has the potential to prevent not only in vitro platelet aggregation but also in vivo thrombus formation and indicate that the highly selective PDE 3 inhibitory effect of NSP-513 may make this compound useful for assessing the physiological role of PDE 3.

PMID: 10887949 [PubMed - indexed for MEDLINE]

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